Am J Transl Res 2023;15(7):4805-4812
www.ajtr.org /ISSN:1943-8141/AJTR0150093

Case Report

Durable responses to TAS-102 plus bevacizumab and TACE in salvage-line treatment of KRAS-mutated and MSS metastatic colorectal cancer: a case report

Wensi Zhao[1], Jian Song[2]

[1]Department of Clinical Oncology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China; [2]Department of Clinical Pharmacy, Renmin Hospital of Wuhan University, Wuhan, Hubei, China

Received March 12, 2023; Accepted June 14, 2023; Epub July 15, 2023; Published July 30, 2023

Abstract: Patients with KRAS-mutated and microsatellite-stable (MSS) metastatic colorectal cancer (mCRC) often have limited options in salvage-line treatment. Reasonable combination strategy may be a valuable exploration. Here, we report a patient with KRAS-mutated and MSS metastatic rectal adenocarcinoma at stage IVB. After failure of previous standard treatment, a durable stable disease was achieved under the fifth-line treatment of TAS-102 plus bevacizumab and transcatheter arterial chemoembolization (TACE). To date, the patient had a PFS of more than 11.6 months with significantly declined tumor markers, alleviated clinical symptoms and improved quality of life. This case suggests that TAS-102 combined with re-challenged bevacizumab and well-timed TACE intervention is an effective strategy for KRAS-mutated and MSS mCRC, with good tolerance and manageable safety, even following disease progression on prior fruquintinib and regorafenib therapies.

Keywords: Metastatic colorectal cancer (mCRC), KRAS mutation, microsatellite-stable (MSS), TAS-102, bevacizumab, transcatheter arterial chemoembolization (TACE), case report

Introduction

Colorectal cancer (CRC) ranks in the top three most common cancers and in the top two in terms of mortality globally [1]. Approximately 20% of CRC patients are diagnosed with metastatic CRC (mCRC) at their initial diagnosis and 50% of localized CRC patients will further develop mCRC [2]. After decades of clinical trials, a significant survival improvement has been achieved with the addition of targeted therapy using 5-fluorouracil based doublet or triplet chemotherapy in mCRC [3, 4]. Supported by high-level evidence-based clinical studies, the standard first- and second-line treatment for mCRC has gained a consensus among gastrointestinal oncologists around the world.

As for the third- and later-line treatment for mCRC in the era of precision medicine, low-frequency or rare gene alterations include BRAF V600E mutation, HER2 overexpression, NTRK rearrangement and DNA mismatch-repair genes deficit (dMMR), etc., needed to be listed separately for specific molecular target drugs or immune checkpoint inhibitors [5]. Next, for the remaining majority of microsatellite-stable (MSS) mCRC patients, regorafenib, trifluridine/tipiracil (FTD/TPI, TAS-102) and fruquintinib were recommended as the third-line treatments in clinical guidelines [6-8]. However, the median progression free survival (mPFS) was only about 2-3 months, which clearly did not meet current clinical needs [9-11].

Exploration of effective combinations has been proved to be an important way to achieve higher clinical activity. In REGONIVO study, advanced CRC patients treated with regorafenib plus nivolumab yielded a mPFS of 7.9 months [12]. Yoshida et al. reported that TAS-102 plus bevacizumab exhibited superiority over TAS-102 monotherapy in third-line treatment of mCRC, with mPFS of 4.5 months [13].

Herein, we report a KRAS-mutated and MSS mCRC patient who achieved a durable stable disease with the salvage-line treatment of TAS-

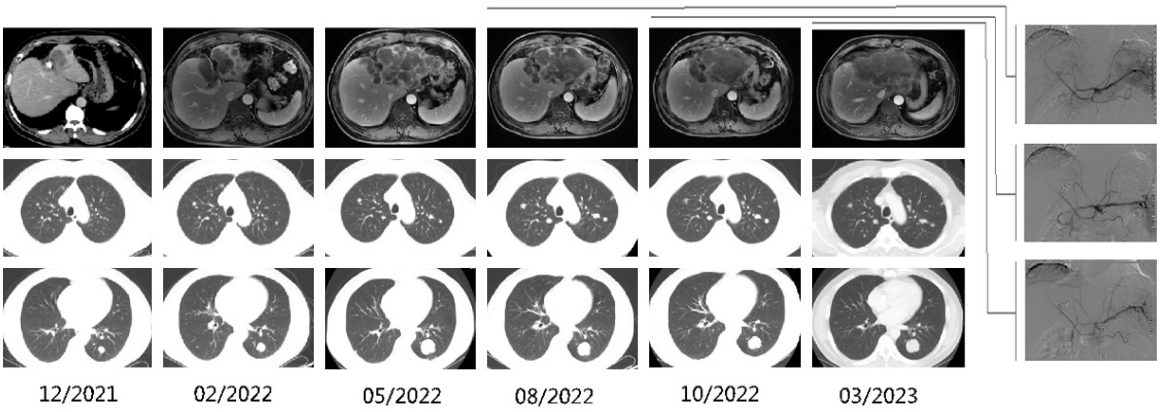

Figure 1. Representative images over the course of therapy. MRI imaging in the first row and CT imaging in the second and third rows showed a continued progression of the left liver lesions and the metastases in both lungs after three cycles of fruquintinib plus tislelizumab and two cycles of regorafenib plus raltitrexed and oxaliplatin chemotherapy from December 2021 to May 2022, followed by a durable stable disease under eleven cycles of TAS-102 in combination with fifteen cycles of bevacizumab and three TACEs in salvage-line treatment from May 2022 to April 2023. The pictures on the right demonstrated the hepatic arteriography of the three irinotecan-TACE procedures in sequence.

102 plus bevacizumab and transcatheter arterial chemoembolization (TACE). We present the case in accordance with the CARE reporting checklist.

Case presentation

A 40-year-old young man presented with abdominal pain and distension, diarrhea, tenesmus and mucoid stools without obvious predisposing factors in April 2018. He had a history of smoking and drinking. The patient was 177 cm tall, weighed 88 kg and had a body mass index (BMI) of 28.09 kg/m^2. The ECOG PS score was 0. After colonoscopy and biopsy in June 2018, he was diagnosed with rectal adenocarcinoma that was approximately 15 cm away from the anus. Then he was admitted to the Department of Gastrointestinal Surgery on June 9, 2018 for a laparoscopic radical resection for rectal cancer. The postoperative histopathological and genetic tests indicated that the patient had moderately differentiated rectal adenocarcinoma (pT3N2aM0, stage IIIB) with proficient mismatch repair (pMMR)/MSS phenotype and KRAS G12C mutation. Next generation sequencing (NGS) was not performed due to personal choice. From July 2018 to October 2018, the patient received six cycles of FOLFOX adjuvant chemotherapy.

The first disease progression (PD) was reported in October 2019 with a new low-density lesion in the left lobe of the liver. Then the patient received six cycles of CAPEOX plus bevacizumab as first-line treatment for mCRC (pT3N2aM1a, stage IVA). The best response was evaluated as partial response (PR). On April 21, 2020, the patient underwent a CT-guided radioactive seed implantation in the liver metastasis with a total of 20 iodine-125 particles of 0.8 mci activity, followed by 5 cycles of capecitabine plus bevacizumab consolidation therapy.

In May 2021, the patient developed right upper abdominal pain. Imaging showed increased liver metastases, and PD was assessed again. Seven cycles of XELIRI plus bevacizumab was administered from May 2021 to November 2021. Best response was evaluated as PR once again. However, thoracic CT in December 2021 suggested new nodules in both lungs; thus, the disease was assessed as a third PD.

After informed consent, the patient participated in a clinical trial and received the combination of fruquintinib (5 mg, po, 3w on/1w off, q4w) plus tislelizumab (200 mg, ivgtt, q3w) from December 16, 2021. During the treatment, the patient developed adverse events (AEs) of grade 1 hand-foot skin reaction, hoarseness, fatigue, and appetite loss and grade 2 immune enteritis, which was recovered after appropriate hormonal and antibiotic therapy. Disease progressed after three cycles of above treatment (**Figure 1**). The patient then withdrew from the study and received regorafenib (160 mg, po, 3w on/1w off, q4w) plus

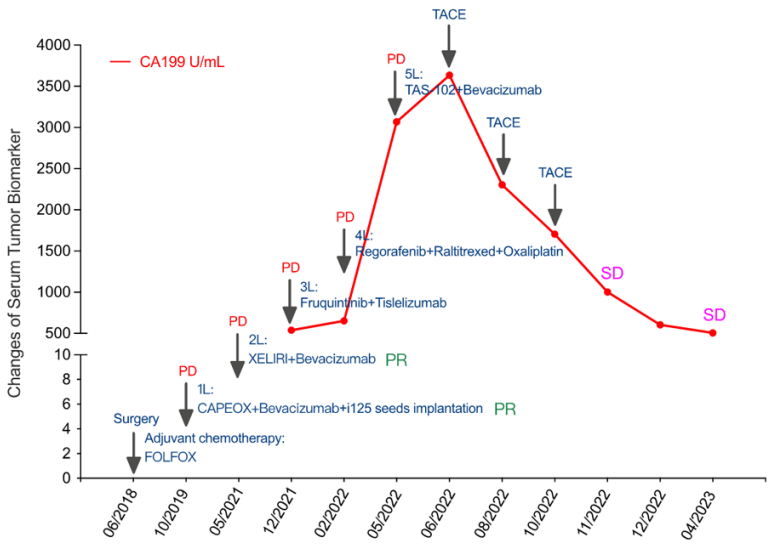

Figure 2. Dynamic changes of serum tumor markers in this patient over the course of therapy. CAPEOX, capecitabine/oxaliplatin; CA199, carbohydrate antigen 199; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin; L, line of therapy; PD, progressive disease; PR, partial response; TACE, transcatheter arterial chemoembolization; SD, stable disease; TAS-102: trifluridine/tipiracil.

raltitrexed (3 mg/m^2, ivgtt, q3w) and oxaliplatin (130 mg/m^2, ivgtt, q3w) from February 25, 2022. After two cycles of treatment, the imaging demonstrated that the liver and lung metastases continued to progress (**Figure 1**). In addition to grade 3 myelosuppression, the patient's intolerance to the triple therapy included palpitation, shortness of breath, chest tightness, intermittent fever, hepatalgia, anal distending pain, hypoproteinemia, and weight loss of nearly 10 kg. Besides, the patient reported a sexual dysfunction since the combination therapy.

A multidisciplinary discussion was conducted to determine the next therapy. TAS-102 plus bevacizumab was recommended. After two cycles of TAS-102 (35 mg/m^2, po, bid, days 1-5 and 8-12, q4w) plus bevacizumab (7.5 mg/kg, ivgtt, q3w) treatment, the patient reported that the anal distending pain was relieved remarkably and the frequency of fever was decreasing. In order to increase the efficacy without compromising quality of life (QoL), we used irinotecan-based TACE to enhance the local control. On June 29, 2022, the patient received his first TACE. The grade 1 post-embolization syndrome (PES) of pain and nausea was quickly alleviated by symptomatic anti-inflammatory, acid suppression and analgesia. After imaging evaluation, apparently fused and necrotic liver lesions were clearly observed (**Figure 1**). Next, the patient received irinotecan-TACE on August 8, 2022 and once again on October 13, 2022. Meanwhile, he continued TAS-102 plus bevacizumab treatment. As of April 22, 2023, the patient had completed eleven cycles of TAS-102 and fifteen cycles of bevacizumab treatment. The latest response was evaluated as a stable disease (SD) without obvious progression of residual metastases and emergence of any new lesions. In terms of safety, only grade 1-2 neutropenia and anemia were observed. No unexpected drug-related toxicity occurred.

After two cycles of treatment, CA199 decreased significantly from 3069.15 U/mL to 2303.18 U/mL, 1705.58 U/mL, 1002.05 U/mL, 604.06 U/mL and 506.7 U/mL (**Figure 2**). A Quality-of-Life (QoL) questionnaire was surveyed on the patient, and the data showed a substantial improvement in health status with respect to role function, cognitive function, emotional function and social function and a relief of symptoms such as fatigue, upper abdominal pain, nausea, vomiting, dyspnea, insomnia, appetite loss, constipation and diarrhea (**Figure 3A** and **3B**). The patient is now continuing the current treatment. Periodic imaging examinations indicated that the patient's disease remained stable with a PFS of more than 11.6 months. The timeline of the whole clinical treatment course was shown in **Figure 4**.

Discussion

This is the first report demonstrating that a young mCRC patient with KRAS mutation and MSS phenotype achieved a durable SD under a fifth-line treatment with TAS-102 plus bevacizumab and TACE after successive failures of prior fruquintinib and regorafenib administration.

Effective first-line treatment is crucial to the clinical outcomes of mCRC. The patient achieved the maximum clinical benefit with a PFS of

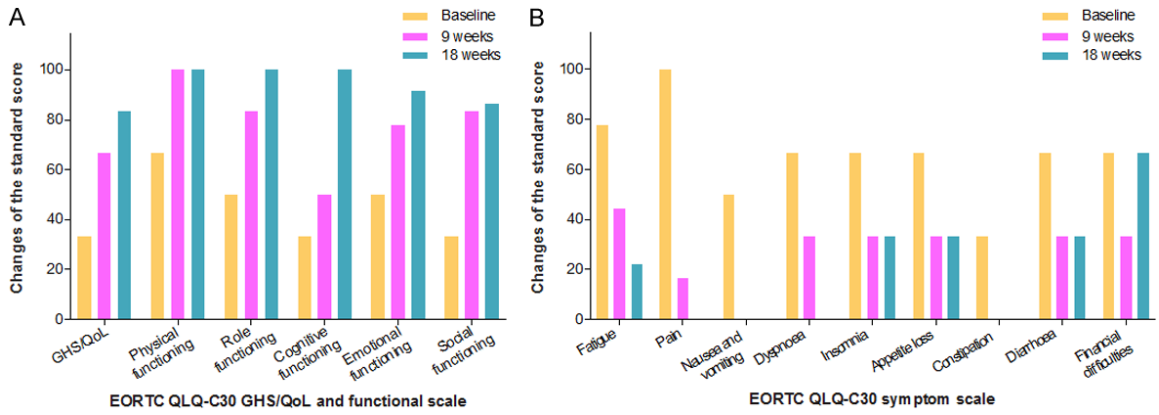

Figure 3. Changes in standard scores on GHS/QoL and functional scales (A) and symptom scales (B) from baseline to week 9 and week 18. Higher GHS/QoL and functional subscale scores represent better health status and functioning, whereas higher symptom subscale scores indicate more severe symptoms and worse health. EORTC QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30; GHS/QoL: general health status/quality of life.

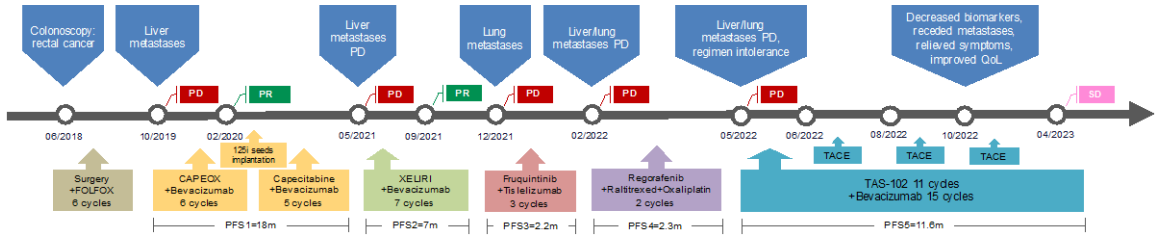

Figure 4. Timeline of the clinical course. CAPEOX, capecitabine/oxaliplatin; FOLFOX, folinic acid/5-fluorouracil/oxaliplatin; PD, progressive disease; PR, partial response; QoL, quality of life; SD, stable disease; TACE, transcatheter arterial chemoembolization; TAS-102: trifluridine/tipiracil; XELIRI, xeloda/irinotecan.

18 months in the first-line treatment with CAPEOX plus bevacizumab. To solidify the treatment effect and delay disease progression, capecitabine plus bevacizumab was administrated as maintenance therapy. It is well known that tumor-induced neoangiogenesis is an important molecular event in the process of tumor occurrence, invasion and metastasis [14]. Sustained antiangiogenic therapy is particularly important in maintaining tumor regression. Clinical studies have shown that bevacizumab beyond PD can still provide survival benefits for mCRC [15]. In this case, the patient received second-line XELIRI plus bevacizumab beyond PD and, as expected, another 7 months of PFS were obtained.

When it comes to the third-line treatment of MSS mCRC without rare gene mutation, in fact, only fruquintinib, regorafenib and TAS-102 are currently available options [5].

Fruquintinib, a highly selective VEGFR inhibitor, was approved for third-line treatment for mCRC with a mPFS of 3.7 months and mOS of 9.3 months in FRESCO study [11]. The FRESCO-2 study once again confirmed the survival benefit of fruquintinib in mCRC population worldwide [16]. Although immunomonotherapy showed an objective response rate (ORR) of 0% in MMS mCRC, a potential synergistic effect of anti-PD-1 plus anti-VEGFR therapy has been reported recently. A phase Ib study of fruquintinib plus sintilimab for MSS mCRC published in the 2021 ASCO conference showed a mPFS of 5.6 months and an ORR of 22.7% [17]. A real-world study of fruquintinib in combination with PD-1 inhibitor in MSS mCRC patients showed an ORR of 11.1% and a mPFS of 3.8 months [18]. On these bases, the patient received three cycles of fruquintinib plus tislelizumab. However, no regression of metastases or reduction of tumor markers was observed. The PFS was merely 2.2 months. The ECOG PS score of the patient at that time was 1. He had a BMI of 26.81 kg/m^2 under a weight of 84 kg. There were no nutritional risk factors or other external conditions that could affect the efficacy. Thus, the

RAS status of the tumor itself may be an intrinsic driver of the poor response, as KRAS mutations are generally associated with higher aggressiveness and worse outcomes [19].

Unlike fruquintinib, regorafenib is a small-molecule multikinase inhibitor. It can simultaneously target several cytokines and cell signals, including inhibiting VEGFR, PDGFR and FGFR for anti-angiogenesis and anti-metastasis, blocking c-KIT, BRAF and RET for anti-proliferation, and interfering with CSF1R for remodeling immunosuppressive microenvironment [20]. In preclinical models, the broad kinase inhibition was able to translate into effective antitumor effects, regardless of RAS and BRAF status. However, the efficacy of regorafenib monotherapy was limited for mCRC in third-line and above settings, with mPFS of 1.9 to 3.2 months [9, 21]. Results from some retrospective studies have shown a survival benefit from regorafenib plus chemotherapy [22]. From this, the patient was treated with regorafenib plus raltitrexed and oxaliplatin. Unfortunately, the disease continued to progress without any tendency to regression. The ECOG PS score of the patient rose to 2 at that time. Cardiac insufficiency and pleural effusion made it impossible for the patient to walk long distances. Accompanied by intermittent fever, hepatic pain, appetite loss and grade 3 leukopenia and thrombocytopenia, the patient lost 5 kg, with a corresponding decrease in BMI to 25.22 kg/m^2. Finally, the patient discontinued the regimen due to intolerance, with a PFS of only 2.3 months.

After a short period of continuous PD, the patient became resistant and intolerant to fruquintinib and regorafenib based therapies. In this gloomy scenario, salvage TAS-102 was considered. TAS-102 is an orally bioavailable modified fluoropyrimidine composed of trifluridine and tipiraci (FTD/TPI). Yoshino first investigated the efficacy and safety of TAS-102 in heavily pretreated mCRC patients in a Japanese phase 2 trial [23]. And then TAS-102 was first approved for refractory mCRC in Japan in March 2014 [24]. The subsequent approval of TAS-102 in USA, Europe and China was due to the results of the pivotal RECOURSE trial [10]. In this trial, the mOS improved from 5.3 to 7.1 months (P<0.001) and mPFS from 1.7 to 2.0 months (P<0.001) with TAS-102 administration. Another randomized, double-blind, placebo-controlled, phase III TERRA study also showed a significant survival benefit in Asian mCRC patients receiving TAS-102 monotherapy (hazard ratio (HR) for death, 0.79; 95% CI, 0.62 to 0.99; P=0.035) compared with placebo, regardless of exposure to prior biologic therapies [25].

Becherirat et al. reported that bevacizumab should be maintained in the whole-process management of mCRC, because the withdrawal of antiangiogenic drugs could induce tumor regrowth and increase resistance [26]. Addition of bevacizumab to TAS-102 demonstrated improved PFS, OS, and disease control with manageable safety in heavily pretreated mCRC patients, regardless of RAS status [13, 27]. Recently, in the global phase III SUNLIGHT trial presented at the 2023 ASCO-GI cancers symposium, FTD/TPI plus bevacizumab provided a statistically significant and a clinically meaningful 3.3-month improvement in OS, extending mOS up to 10.8 months, with a 3.2-month improvement in PFS and a 39% reduction in the HR of death in refractory mCRC patients [28].

Locoregional therapies can enhance disease control and improve QoL. In the CIREL study, irinotecan-TACE was demonstrated to be a safe, effective, feasible and high technical success rate tool for mCRC patients with liver-only or liver-dominant metastases [29]. TACE combined with bevacizumab has been reported to improve survival and delay disease progression in mCRC [30]. To consolidate the hard-won antitumor effect, TACE was introduced to the patient. So far, the patient has successfully received three TACE without severe PES and is scheduled to receive next TACE if needed. To date, he has achieved a PFS of more than 11.6 months with significant improvement in clinical symptoms and QoL.

Growing evidence suggests that mCRC patients with KRAS G12C mutation have higher rates of basal EGFR activation and correspondingly worse PFS and OS compared with KRAS non-G12C patients [31]. If disease progresses again, adagrasib plus cetuximab may be recommended and/or the patient may be advised to undergo NGS for other potential therapeutic targets such as anti-HER2-targeted therapies [32-34].

In short, the cooperative effect of TAS-102 plus bevacizumab and TACE was demonstrated in this case. After treatment, the tumor burden of the young patient was significantly relieved with respect to the complete remission of anal distending pain and hepatalgia, extensive fusion and necrosis of liver metastases, and obvious reduction of serum CA199. In addition, the patient's QoL was also improved, as evidenced by the relief of mental stress and improvement of health status and organic functions. Except for chemotherapy-induced neutropenia and anemia of grade 1-2, no new safety signals were noted. In brief, the combination strategy provided a satisfactory efficacy with a predictable and manageable safety profile, and it can be actively applied in clinical practice for heavily pretreated mCRC patients with KRAS mutation and MSS phenotype.

However, many questions remain to be resolved. First, primary or acquired resistance to this treatment remains a challenge in clinical practice. Second, more in-depth research is needed to establish a reliable set of biomarkers including but not limited to the liquid biopsy indicators such as circulating tumor cell or circulating tumor DNA for selecting right patients and monitoring therapeutic effect. Third, strengthening the collaboration of multidisciplinary teams remains an important part of the optimal clinical decision making for each mCRC patient. And finally, studies with larger samples are still needed.

Conclusion

We report a case of a KRAS-mutated and MSS mCRC patient who achieved a durable SD and had a PFS of more than 11.6 months after TAS-102 combined with bevacizumab and TACE therapy. This case indicates that mCRC patient can still respond to TAS-102-based combination therapy even after prior fruquintinib and regorafenib failure. The angiogenesis inhibitor and TACE, as effective tumor microenvironment modulators, may be important components of the synergistic efficacy for mCRC in salvage-line setting.

Acknowledgments

The authors thank the patient and his caregivers for allowing us to publish his clinical case. This work was supported by the National Natural Science Foundation of China (No. 82102954).

Written informed consent was obtained from the patient for the publication of any potentially identifiable images or data included in this case report.

Disclosure of conflict of interest

None.

Address correspondence to: Wensi Zhao, Department of Clinical Oncology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuchang District, Wuhan 430060, Hubei, China. Tel: +86-27-88041911 Ext. 81338; E-mail: zhaowensi@bjmu.edu.cn

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